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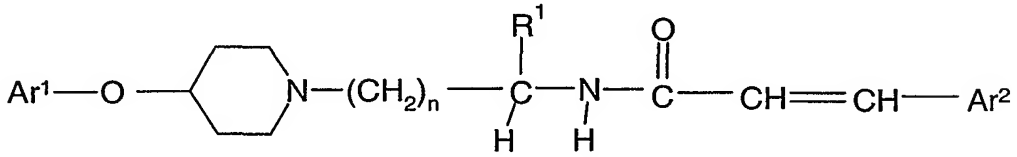
(54) Title: N-(4-ARYLOXYPIPERIDIN-1-YLALKYL) CINNAMIC AMIDES AS CCR3 RECEPTOR ANTAGONISTS

(57) Abstract: Compounds of formula (I) in free or salt form, where Ar^1 is phenyl substituted by one or more substituents selected from halogen, cyano, nitro, and C_1-C_8-alkyl optionally substituted by cyano or halogen, Ar^2 is phenyl or naphthyl which is substituted by one or more substituents selected from halogen, cyano or C_1-C_8-alkoxy, R^1 is hydrogen or C_1-C_8-alkyl, and n is 1, 2, 3 or 4. The compounds are useful as pharmaceuticals.

N-(4-ARYLOXYPIRIDIN-1-YLALKYL) CINNAMIC AMIDES AS CCR3 RECEPTOR ANTAGONISTS

This invention relates to organic compounds, their preparation and their use as pharmaceuticals.

In one aspect, the invention provides compounds of formula



I

in free or salt form, where

Ar^1 is phenyl substituted by one or more substituents selected from halogen, cyano, nitro, and C_1-C_8-alkyl optionally substituted by cyano or halogen,

Ar^2 is phenyl or naphthyl which is substituted by one or more substituents selected from halogen, cyano or C_1-C_8-alkoxy,

R^1 is hydrogen or C_1-C_8-alkyl, and

n is 1, 2,3 or 4.

Terms used in the specification have the following meanings :

"C_1-C_8-alkyl" as used herein denotes straight chain or branched C_1-C_8-alkyl, which may be, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, straight or branched pentyl, straight or branched hexyl, straight or branched heptyl, or straight or branched octyl. Preferably, C_1-C_8-alkyl is C_1-C_4-alkyl.

"C_1-C_8-alkoxy" as used herein denotes straight chain or branched C_1-C_8-alkoxy which may be, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, straight or branched pentoxy, straight or branched hexyloxy, straight or branched heptyloxy, or straight or branched octyloxy. Preferably, C_1-C_8-alkoxy is C_1-C_4-alkoxy.

"Halogen" as used herein may be fluorine, chlorine, bromine or iodine; preferably it is fluorine, chlorine or bromine.

Ar^1 as substituted phenyl may be substituted, for example, by one, two or three substituents, preferably one or two substituents, preferably selected from fluorine, chlorine, bromine,

nitro, C_1-C_4-alkyl and cyano-C_1-C_4-alkyl, especially fluorine or chlorine. When there is one substituent, it is preferably para to the indicated ether group. When there is more than one substituent, preferably one is para to the indicated ether group.

Ar^2 as substituted phenyl may, for example, be substituted by one, two, three, four or five, preferably by one, two or three, substituents as hereinbefore described. Ar^2 may be, for example, monosubstituted phenyl in which the substituent, preferably halogen, cyano or C_1-C_4-alkoxy, is preferably ortho or meta to the indicated -CH=CH- group. Ar^2 may alternatively be, for example, disubstituted phenyl in which the substituents are preferably selected from halogen, cyano and C_1-C_4-alkoxy, especially one halogen and one C_1-C_4-alkoxy, or one cyano and one C_1-C_4-alkoxy. Ar^2 may alternatively be, for example, trisubstituted phenyl in which the substituents are preferably selected from halogen and C_1-C_4-alkoxy or penta-substituted phenyl in which the substituents are preferably halogen, especially fluorine. Especially preferred groups Ar^2 are disubstituted phenyl where one substituent is C_1-C_4-alkoxy, preferably ortho to the -CH=CH- group, and the other, preferably para to the C_1-C_4-alkoxy group, is halogen, especially chlorine or bromine, or cyano.

Preferred compounds of formula I in free or salt form include those in which
Ar^1 is phenyl which is substituted by one or two substituents selected from halogen, nitro, or C_1-C_4-alkyl optionally substituted by cyano, one of said substituents preferably being para to the indicated ether group,
Ar^2 is phenyl substituted by one or two substituents selected from C_1-C_4-alkoxy, halogen and cyano,
R^1 is hydrogen or C_1-C_4-alkyl, and
n is 1 or 2.

Further preferred compounds of formula I in free or salt form include those in which
Ar^1 is phenyl which is substituted by fluorine or chlorine para to the indicated ether group and optionally substituted by one further substituent selected from fluorine, chlorine, nitro or C_1-C_4-alkyl,
Ar^2 is phenyl which is substituted ortho to the indicated -CH=CH- group by C_1-C_4-alkoxy and para to the C_1-C_4-alkoxy group by halogen, especially bromine, or cyano,
R^1 is hydrogen and
n is 1.

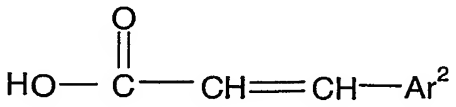
The compounds represented by formula I are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids, for example aliphatic monocarboxylic acids such as formic acid, acetic acid, trifluoroacetic acid, propionic acid and butyric acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as maleic acid or succinic acid, aromatic carboxylic acids such as benzoic acid, p-chlorobenzoic acid, diphenylacetic acid or triphenylacetic acid, aromatic hydroxy acids such as o-hydroxybenzoic acid, p-hydroxybenzoic acid, 1-hydroxynaphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2-carboxylic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid. These salts may be prepared from compounds of formula I by known salt-forming procedures.

When R^1 is other than hydrogen, the carbon atom to which R^1 is attached in formula I is asymmetric, in which case the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. The invention embraces both individual optically active R and S isomers as well as mixtures, e.g.racemic or diastereomeric mixtures, thereof. For pharmaceutical use in accordance with the invention, the R isomer is generally preferred.

Specific especially preferred compounds of the invention are those described hereinafter in the Examples.

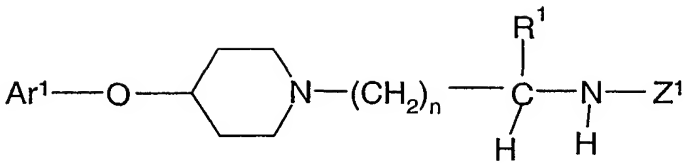
The invention also provides a process for the preparation of compounds of formula I which comprises

(i) reacting a compound of formula



II

or an amide-forming derivative thereof, where Ar^2 is as hereinbefore defined, with a compound of formula



III

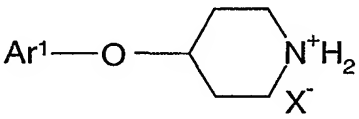
where Ar^1, R^1 and n are as hereinbefore defined and Z^1 denotes a solid phase substrate chemically linked to the indicated nitrogen atom, and detaching the resulting product from the substrate to replace Z^1 by hydrogen; and

(ii) recovering the product in free or salt form.

The above process may be effected using known methods, for example by reacting the substrate-bound compound with the free acid under known peptide coupling conditions, for example in the presence of a tertiary amine and a peptide coupling agent such as a phosphonium salt, a uronium salt such as O-(7-azabenzotriazol-1-yl)-N,N,N^1,N^1-tetramethyluronium hexafluorophosphate, or diisopropylcarbodiimide. The reaction may be effected in an inert organic solvent such as dimethylformamide (DMF). Suitable reaction temperatures are from 0 to 40°C, e.g. 15 to 25°C. The product may be detached from the substrate in a known manner, for example, where the N atom is linked to a CH_2 of a benzyl group in Z^1, by treatment with trifluoroacetic acid (TFA).

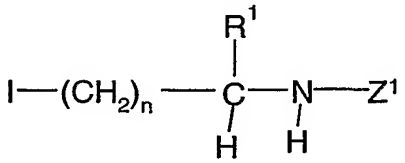
Compounds of formula II are either available commercially or may be prepared by known methods.

Compounds of formula III may be prepared by reacting a compound of formula



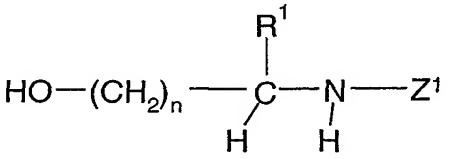
IV

where Ar^1 is as hereinbefore defined, X is the residue of an acid, particularly a carboxylic acid such as trifluoroacetic acid, after removal of an acidic hydrogen atom therefrom, with a compound of formula



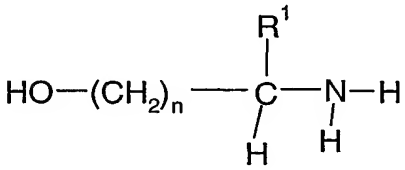
V

where R^1, Z^1 and n are as hereinbefore defined, for example using known procedures such as reaction in an inert organic solvent such as DMF in the presence of a tertiary amine, conveniently at a temperature of 40 to 60°C. Compounds of formula V may be prepared by reaction of a compound of formula



VI

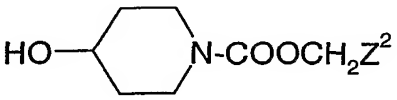
where R^1, Z^1 and n are as hereinbefore defined, with iodine, for example using known procedures such as reaction in an inert organic solvent such as a mixture of THF and acetonitrile in the presence of a triarylphosphine and imidazole, conveniently at a temperature of 10 to 40°C. Compounds of formula VI may be prepared by reaction of a compound of formula



VII

where R^1 and n are as hereinbefore defined, with a solid phase substrate Z^1 having a group, such as an aldehyde group, reactive with amino. Such solid phase substrates, including modified resins, particularly modified polystyrene resins such as a modified polystyrene having a p-formyl-substituted phenoxyalkyl group attached to skeletal benzene rings of the polystyrene, are commercially available. Compounds of formula VII are known or may be prepared by known methods.

Compounds of formula IV may be prepared by reacting a compound of formula Ar^1OH with a compound of formula

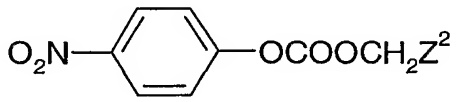


VIII

where Ar^1 is as hereinbefore defined and Z^2 denotes a solid phase substrate chemically linked to the indicated methylene group, diethyldiazodicarboxylate and a triarylphosphine (Mitsunobu reaction), and reacting the resulting product with an acid HX where X is as hereinbefore defined to detach the product from the substrate and replace $COOCH^2Z^2$ by

two hydrogen atoms. The reaction is conveniently carried out in an organic solvent, for example an ether such as THF. The Mitsunobu reaction temperature may suitably be from 10 - 50°C, conveniently room temperature. The product may be detached from the substrate in a known manner, for example by treatment with trifluoroacetic acid.

Compounds of formula VIII may be prepared by reaction of 4-hydroxypiperidine with a compound of formula



IX

where Z^2 is as hereinbefore defined. The reaction may suitably be carried out in an inert organic solvent, for example a halohydrocarbon such as dichloromethane (DCM). Suitable reaction temperatures may be from 10 - 50°C, conveniently room temperature.

Compounds of formula IX may be prepared by reacting p-nitrophenyl chloroformate with a compound of formula

$$HOCH_2Z^2 \qquad X$$

where Z^2 is as hereinbefore defined. This reaction may be carried out in the presence of a tertiary base such as N-methylmorpholine and in an inert solvent such as DCM. Resin-based compounds of formula X are commercially available, for example as modified polystyrene resins such as Wang resin having a p-hydroxymethyl-substituted phenoxyalkyl group attached to skeletal benzene rings of the polystyrene.

Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallization. Compounds of formula I can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional crystallization or asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

Compounds of formula I in free or pharmaceutically acceptable salt form, hereinafter referred to alternatively as agents of the invention, are useful as pharmaceuticals.

Accordingly the invention also provides a compound of formula I in free or pharmaceutically acceptable salt form for use as a pharmaceutical. The agents of the invention act as CCR-3 receptor antagonists, thereby inhibiting the infiltration and activation of inflammatory cells, particularly eosinophils, and inhibiting allergic response. The inhibitory properties of agents of the invention can be demonstrated in the following assay :

CCR-3 Binding Assay

In this assay the effect of agents of the invention on the binding of human eotaxin to human CCR-3 is determined. Recombinant cells expressing human CCR-3 are captured by wheatgerm agglutinin (WGA) polyvinyltoluidene (PVT) SPA beads (available from Amersham), through a specific interaction between the WGA and carbohydrate residues of glycoproteins on the surface of the cells. [^{125}I]-human eotaxin (available from Amersham) binds specifically to CCR-3 receptors bringing the [^{125}I]-human eotaxin in close proximity to the SPA beads. Emitted â-particles from the [^{125}I]-human eotaxin excite, by its proximity, the fluorophore in the beads and produce light. Free [^{125}I]-human eotaxin in solution is not in close proximity to the scintillant and hence does not produce light. The scintillation count is therefore a measure of the extent to which the test compound inhibits binding of the eotaxin to the CCR-3.

Preparation of Assay Buffer: 5.96 g HEPES and 7.0 g sodium chloride are dissolved in distilled water and 1M aqueous $CaCl_2$ (1 mL) and 1M aqueous $MgCl_2$ (5 mL) are added. The pH is adjusted to 7.6 with NaOH and the solution made to a final volume of 1 L using distilled water. 5 g bovine serum albumin and 0.1 g sodium azide are then dissolved in the solution and the resulting buffer stored at 4°C. A Complete™ protease inhibitor cocktail tablet (available from Boehringer) is added per 50 mL of the buffer on the day of use.

Preparation of Homogenisation Buffer: Tris-base (2.42g) is dissolved in distilled water, the pH of the solution is adjusted to 7.6 with hydrochloric acid and the solution is diluted with distilled water to a final volume of 1L. The resulting buffer is stored at 4°C. A Complete™ protease inhibitor cocktail tablet is added per 50 mL of the buffer on the day of use.

Preparation of membranes: Confluent rat basophil leukemia (RBL-2H3) cells stably expressing CCR3 are removed from tissue culture flasks using enzyme-free cell dissociation buffer and resuspended in phosphate-buffered saline. The cells are centrifuged (800 g, 5 minutes), the pellet resuspended in ice-cold homogenisation buffer using 1 mL

homogenisation buffer per gram of cells and incubated on ice for 30 minutes.The cells are homogenised on ice with 10 strokes in a glass mortar and pestle.The homogenate is centrifuged (800 g, 5 minutes, 4°C), the supernatant further centrifuged (48,000 g, 30 minutes, 4°C) and the pellet redissolved in Homogenisation Buffer containing 10% (v/v) glycerol.The protein content of the membrane preparation is estimated by the method of Bradford (Anal.Biochem. (1976) 72:248) and aliquots are snap frozen and stored at –80°C.

The assay is performed in a final volume of 250 µL per well of an Optiplate (ex Canberra Packard). To selected wells of the Optiplate are added 50 µL of solutions of a test compound in Assay Buffer containing 5 % DMSO (concentrations from 0.01nM to 10 µM). To determine total binding, 50 µL of the Assay Buffer containing 5 % DMSO is added to other selected wells. To determine non-specific binding, 50 µL of 100nM human eotaxin (ex R&D Systems) in Assay Buffer containing 5 % DMSO is added to further selected wells. To all wells are added 50 µL [^{125}I]-Human eotaxin (ex Amersham) in Assay Buffer containing 5 % DMSO at a concentration of 250 pM (to give a final concentration of 50 pM per well), 50 µL of WGA-PVT SPA beads in Assay Buffer (to give a final concentration of 1.0mg beads per well) and 100 µL of the membrane preparation at a concentration of 100 µg protein in Assay Buffer (to give a final concentration of 10 µg protein per well). The plate is then incubated for 4 hours at room temperature. The plate is sealed using TopSeal-S (ex Canberra Packard) according to the manufacturer's instructions. The resulting scintillations are counted using a Canberra Packard TopCount, each well being counted for 1 minute. The concentration of test compound at which 50% inhibition occurs (IC_{50}) is determined from concentration-inhibition curves in a conventional manner.

The compounds of the Examples hereinbelow have IC_{50} values of the order of 1µM or less in the above assay. For instance, the compounds of Examples 12 and 13 have IC_{50} values of 47 nM and 5 nM respectively.

Having regard to their inhibition of binding of CCR-3, agents of the invention are useful in the treatment of conditions mediated by CCR-3, particularly inflammatory or allergic conditions. Treatment in accordance with the invention may be symptomatic or prophylactic.

Accordingly, agents of the invention are useful in the treatment of inflammatory or obstructive airways diseases, resulting, for example, in reduction of tissue damage, bronchial hyperreactivity, remodelling or disease progression. Inflammatory or obstructive airways

diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, excercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), acute/adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, agents of the invention are also useful in the treatment of eosinophil related disorders, e.g. eosinophilia, in particular eosinophil related disorders of the airways (e.g. involving morbid eosinophilic infiltration of pulmonary tissues) including hypereosinophilia as it effects the airways and/or lungs as well as, for example, eosinophil-related disorders of the airways consequential or concomitant to Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

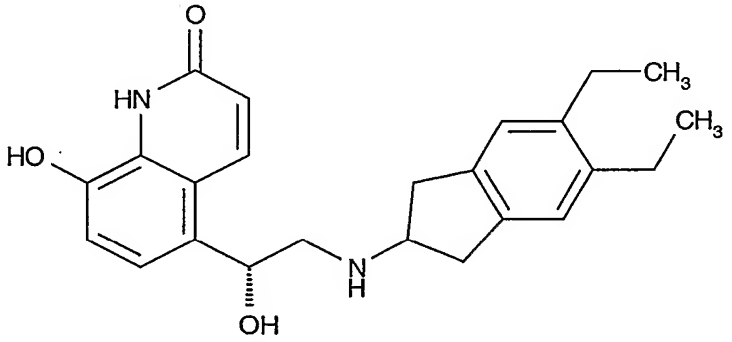
Agents of the invention are also useful in the treatment of inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphisus, epidermolysis bullosa acquisita, and other inflammatory or allergic conditions of the skin.

Agents of the invention may also be used for the treatment of other diseases or conditions, in particular diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory conditions of the gastrointestinal tract, for example inflammatory bowel disease such as ulcerative colitis and Crohn's disease.

The effectiveness of an agent of the invention in inhibiting inflammatory conditions, for example in inflammatory airways diseases, may be demonstrated in an animal model, e.g. a mouse or rat model, of airways inflammation or other inflammatory conditions, for example as described by Szarka et al, J. Immunol. Methods (1997) 202:49-57; Renzi et al, Am. Rev. Respir. Dis. (1993) 148:932-939; Tsuyuki et al., J. Clin. Invest. (1995) 96:2924-2931; and Cernadas et al (1999) Am. J. Respir. Cell Mol. Biol. 20:1-8.

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of

such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance. Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone, fluticasone, ciclesonide or mometasone, LTB4 antagonists such as those described in US5451700, LTD4 antagonists such as montelukast and zafirlukast, dopamine receptor agonists such as cabergoline, bromocriptine, ropinirole and 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]-amino]ethyl]-2(3H)-benzothiazolone and pharmaceutically acceptable salts thereof (the hydrochloride being Viozan® - AstraZeneca), and PDE4 inhibitors such as Ariflo® (GlaxoSmith Kline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), and PD189659 (Parke-Davis). Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide, and beta-2 adrenoceptor agonists such as salbutamol, terbutaline, salmeterol and, especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of PCT International Publication No. WO00/75114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



XI

and pharmaceutically acceptable salts thereof. Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride. Combinations of agents of the invention and steroids, beta-2 agonists, PDE4 inhibitors or LTD4 antagonists may be used, for example, in the treatment of COPD or, particularly, asthma. Combinations of agents of the invention and anticholinergic or antimuscarinic agents, PDE4 inhibitors, dopamine receptor agonists or LTB4 antagonists may be used, for example, in the treatment

of asthma or, particularly, COPD.

Other useful combinations of agents of the invention with anti-inflammatory drugs are those with other anatagonists of chemokine receptors, e.g. CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, particularly CCR-5 antagonists such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D, Takeda antagonists such as N-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5H-benzocyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-N,N-dimethyl-2H-pyran-4-aminium chloride (TAK-770), and CCR-5 antagonists described in US6166037 (particularly claims 18 and 19), WO00/66558 (particularly claim 8), and WO00/66559 (particularly claim 9).

In accordance with the foregoing, the invention also provides a method for the treatment of a condition mediated by CCR-3, for example an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease, which comprises administering to a subject, particularly a human subject, in need thereof an effective amount of a compound of formula I in a free or pharmaceutically acceptable salt form as hereinbefore described. In another aspect the invention provides the use of a compound of formula I, in free or pharmaceutically acceptable salt form, as hereinbefore described for the manufacture of a medicament for the treatment of a condition mediated by CCR-3, for example an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; by inhalation, for example in the treatment of inflammatory or obstructive airways disease; intranasally, for example in the treatment of allergic rhinitis; topically to the skin, for example in the treatment of atopic dermatitis; or rectally, for example in the treatment of inflammatory bowel disease.

In a further aspect, the invention also provides a pharmaceutical composition comprising as active ingredient a compound of formula I in free or pharmaceutically acceptable salt form, optionally together with a pharmaceutically acceptable diluent or carrier therefor. The composition may contain a co-therapeutic agent such as an anti-inflammatory or bronchodilatory drug as hereinbefore described. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches.

Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

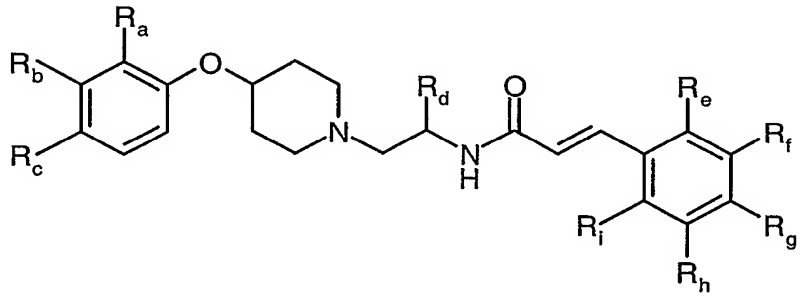
The invention includes (A) an agent of the invention in inhalable form, e.g. in an aerosol or other atomisable composition or in inhalable particulate, e.g. micronised form, (B) an inhalable medicament comprising an agent of the invention in inhalable form; (C) a pharmaceutical product comprising such an agent of the invention in inhalable form in association with an inhalation device; and (D) an inhalation device containing an agent of the invention in inhalable form.

Dosages of agents of the invention employed in practising the present invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of 0.01 to 30 mg/kg while for oral administration suitable daily doses are of the order of 0.01 to 100 mg/kg.

The invention is illustrated by the following Examples.

Examples 1 - 13

Compounds of formula I which are also of formula



XII

are shown in the following table, the method of preparation being described hereinafter. R_d, R_f, R_g and R_i are each hydrogen in all of the Examples. The table also shows characterising mass spectrometry data ([MH]+) and, where the Example is a salt, the identity of the salt-forming acid.

Example No	R_a	R_b	R_c	R_e	R_h	M/S [MH]+	Salt form
1	H	H	F	OCH_2CH_3	Br	492.7	CF_3CO_2H
2	H	H	F	OCH_3	Br	479.6	CF_3CO_2H
3	H	Cl	H	OCH_3	Br	495.3	CF_3CO_2H
4	H	H	NO_2	OCH_3	Br	506.4	CF_3CO_2H
5	H	H	Cl	OCH_3	Br	495.3	CF_3CO_2H
6	H	NO_2	Cl	OCH_3	Br	540.4	CF_3CO_2H
7	H	F	F	OCH_3	Br	495.2	CH_3CO_2H
8	H	CH_3	F	OCH_3	Br	491.2	CF_3CO_2H
9	H	H	F	OCH_3	CN	424.2	CF_3CO_2H
10	F	H	F	OCH_3	CN	442.0	CF_3CO_2H
11	Cl	H	Cl	OCH_3	CN	475.7	CF_3CO_2H
12	H	H	Br	OCH_3	CN	485.7	CF_3CO_2H
13	H	CH_3	Cl	OCH_3	CN	456.6	CF_3CO_2H

Resin Intermediate 1

To Wang resin (ex Novabiochem) (40g, 52mmol) in dichloromethane (DCM) (300ml) is added N-methylmorpholine (17.2ML, 156mmol) followed by 4-nitrophenyl chloroformate (32g, 156mmol) and the resin is stirred at room temperature for 18 hours, then filtered and washed with DCM (4 x 200ml). To the resulting *p*-nitrophenyl carbonate resin (46g, 60mmol) in DCM (400ml) is added 4-hydroxypiperidine (18.2g, 180mmol) and the suspension is shaken for 5 hours at room temperature. The resin obtained is washed with DMF until the filtrates are colourless, then washed with CH_3OH (200ml), DCM (200ml) and finally diethylether (200ml). The resin obtained is dried under vacuum to give a product of formula VIII (IR 1762.76cm^{-1}).

4-(4-Fluorophenoxy)-piperidine

Resin Intermediate 1 (800mg, 1.04mmol) is suspended in THF (10ml) and 4-fluorophenol (350mg, 3.12mmol) is added, followed by triphenylphosphine (818mg, 3.12mmol) and di-*tert*-butyl azodicarboxylate (718mg, 3.12mmol). The suspension is shaken at room temperature for 18 hours then washed in turn with THF, DMF, CH_3OH and DCM (50ml each). To the washed resin is added a mixture of TFA and DCM (95:5 *v/v*) and the suspension is shaken at room temperature for 1 hour. The mixture is then filtered and the filtrates evaporated under vacuum to give the title compound as the TFA salt. $[MH]^+$ 196.3.

Resin Intermediate 2

To a suspension of 2-(formyl-3-methoxyphenoxy)ethyl polystyrene (AMEBA) resin (ex Novabiochem) (6.85g, 3.33mmol) in a mixture of methanol / dichloromethane (60ml, 1:1 *v/v*) is added 2-aminoethanol and sodium triacetoxyborohydride (4.00g, 18.85mmol) and the mixture is shaken for 16 hours at 20°C, then filtered. The resin obtained is washed with methanol, DMF and dichloromethane, then dried under vacuum. A THF / acetonitrile mixture (50ml, 1:1 *v/v*) is added to the dried resin followed by iodine (4.80g, 18.85mmol), imidazole (1.28g, 18.85mmol) and triphenylphosphine (4.90g,18.85mmol).The suspension obtained is shaken for 18 hours at 20°C, then filtered. The resin is washed with THF and dried under vacuum.

***(E)*-3-(5-cyano-2-methoxy-phenyl)-acrylic acid**

To a suspension of palladium(II)acetate (0.77g, 3.42mmol) in *N,N*-dimethylacetamide (375ml) are added tetraethylammonium chloride (19.36g, 114.5mmol), dicyclohexyl methyl amine (35.1g, 174.5mmol), and 3-bromo-4-methoxybenzonitrile (25.51g, 118.0mmol)

under a nitrogen atmosphere. The suspension is heated to 100-105 °C whereupon t-butyl acrylate (14.82g, 114.5mmol) is slowly added over a period of 45 min. After a further 30-60 min stirring at 100°C, the solution is cooled to room temperature and diluted with TBME (375ml). The resulting biphasic mixture is stirred vigorously for 10 min. The (upper) TBME phase is successively washed with water (100ml), 10% aq. citric acid (100ml) and 25% aq. NaCl (100ml). The combined aqueous phases are extracted with TBME (100ml). After adding active charcoal (0.4g), the combined TBME phases are stirred vigorously for 10 min and filtered. Anhydrous Na_2SO_4 (10g) is added and the resulting suspension is stirred for another 10 min and filtered. The filtrate is concentrated to a volume of 50-70ml under reduced pressure and, over a period of 25-30 min, added at room temperature to anhydrous trifluoroacetic acid (150ml). The resulting solution is stirred at room temperature for 60 min (precipitation forms), cooled to 0-5°C in an ice bath, and diluted with ethyl acetate (410ml). After stirring vigorously at 0 °C for an additional 60 min, the suspension is filtered. The residue is dried under vacuum at 45-50°C to give *(E)*-3-(5-cyano-2-methoxy-phenyl)-acrylic acid as a crystalline solid, mp. 252-253°C. MS (ES): $[M-H]^-$ 202.

(*E*)-3-(5-Cyano-2-methoxy-phenyl)-N-{2-[4-(4-fluoro-phenoxy)-piperidin-1-yl]-ethyl}-acrylamide trifluoroacetate - Example 12

To freshly prepared Resin Intermediate 2 (0.30g, 0.48mmol) is added a solution of 4-(4-fluoro-phenoxy)-piperidine (309mg, 1.00mmol) dissolved in DMF (2ml) and diisopropylethylamine (62.4mg; 0.48mmol). The mixture is heated at 55°C for 6 hours and then at room temperature for 3 days. The resulting mixture is filtered and the resin is washed with DMF. To the washed resin are added (*E*)-3-(5-cyano-2-methoxy-phenyl)-acrylic acid (0.27g, 1.05 mmol), O-(7-azabenzotriazol-1-yl)- *N,N,N',N'*-tetramethyl-uroniumhexafluorophosphate (547mg, 1.44mmol) diisopropylethyl-amine (186mg, 1.44 mmol) and DMF (4ml) and the mixture is shaken at 20°C for 18 hours, then washed with DMF and methanol, after which it is treated with trifluoroacetic acid / dichloromethane (6ml, 1:1 *v/v*) at 20°C for 1 hour to remove the product from the resin. The resulting mixture is filtered and the filtrate evaporated under vacuum to give the product, $[MH]^+$ 424.2.

4-(4-Chloro-3-methyl-phenoxy)-piperidine

Resin Intermediate 1 (1.0g, 1.1mmol) is suspended in THF (12ml) and 4-chloro-3-methylphenol (470.5mg, 3.3mmol) is added, followed by triphenylphosphine (866mg, 3.3mmol) and di-*tert*-butyl azodicarboxylate (760mg, 3.3mmol). The suspension is shaken at room temperature for 18 hours then washed in turn with THF, DMF, CH_3OH and DCM

(50ml each). To the washed resin is added a mixture of TFA and DCM (95:5 *v/v*) and the suspension is shaken at room temperature for 1 hour. The mixture is then filtered and the filtrates evaporated under vacuum to give the title compound as the TFA salt. $[MH]^+$ 228.1.

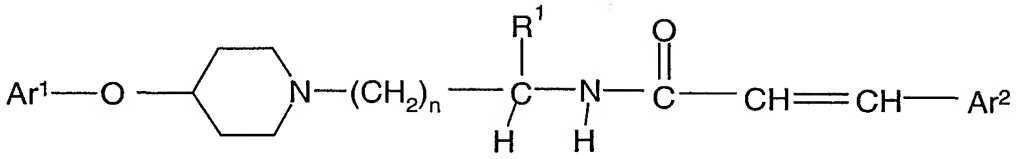
(*E*)-N-{2-[4-(4-Chloro-3-methyl-phenoxy)-piperidin-1-yl]-ethyl}-3-(5-cyano-2-methoxy-phenyl)-acrylamide trifluoroacetate – Example 13

To freshly prepared Resin Intrermediate 2 (0.234g, 0.34mmol) is added a solution of 4-(4-chloro-3-methyl-phenoxy)-piperidine (213mg, 0.63mmol) dissolved in DMF (3.3ml) and diisopropylethylamine (0.34ml, 1.98mmol). The mixture is heated at 55°C for 6 hours and then at room temperature for 3 days. The resulting mixture is filtered and the resin is washed with DMF. To the washed resin are added (*E*)-3-(5-cyano-2-methoxy-phenyl)-acrylic acid (0.122g, 0.60mmol), diisopropylcarbodiimide (76mg, 0.60mmol) and DMF (2ml) and the mixture is shaken at 20°C for 18 hours, then washed with DMF and methanol, after which it is treated with TFA/DCM (6ml, 1:1 *v/v*) at 20°C for 1 hour to remove the product from the resin. The resulting mixture is filtered and the filtrate evaporated under vacuum to give the product, $[MH]^+$ 456.6.

The other Examples are prepared analogously to Examples 12 and 13, using appropriate starting materials.

Claims :

1. A compound of formula



I

in free or salt form, where

Ar^1 is phenyl substituted by one or more substituents selected from halogen, cyano, nitro, and C_1-C_8-alkyl optionally substitued by cyano or halogen,

Ar^2 is phenyl or naphthyl which is substituted by one or more substituents selected from halogen, cyano or C_1-C_8-alkoxy,

R^1 is hydrogen or C_1-C_8-alkyl, and

n is 1, 2,3 or 4.

2. A compound according to claim 1, in which Ar^2 is monosubstituted phenyl in which the substituent is halogen, cyano or C_1-C_4-alkoxy; or disubstituted phenyl in which the substituents are selected from halogen, cyano and C_1-C_4-alkoxy; or trisubstituted phenyl in which the substituents are selected from halogen and C_1-C_4-alkoxy; or penta-substituted phenyl in which the substituents are halogen.

3. A compound according to claim 1, in which

Ar^1 is phenyl substituted by one or two substituents selected from halogen, nitro, or C_1-C_4-alkyl optionally substituted by cyano, one of said substituents preferably being para to the indicated ether group,

Ar^2 is phenyl substituted by one or two substituents selected from C_1-C_4-alkoxy, halogen and cyano,

R^1 is hydrogen or C_1-C_4-alkyl, and

n is 1 or 2.

4. A compound according to claim 1, in which

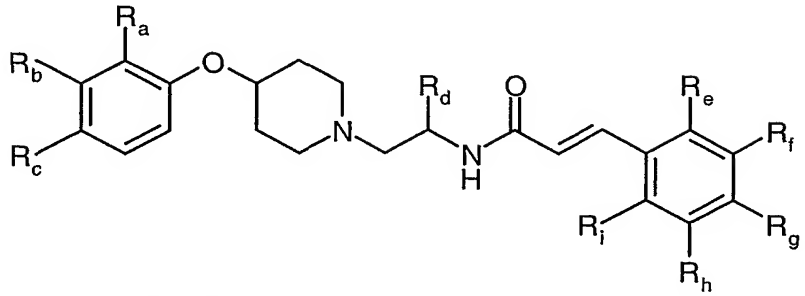
Ar^1 is phenyl which is substituted by fluorine or chlorine para to the indicated ether group and optionally substituted by one further substituent selected from fluorine, chlorine, nitro or C_1-C_4-alkyl,

Ar^2 is phenyl which is substituted ortho to the indicated -CH=CH- group by C_1-C_4-alkoxy and para to the C_1-C_4-alkoxy group by halogen, especially bromine, or cyano,

R^1 is hydrogen and

n is 1.

5. A compound according to claim 1, which is of formula



XII

in free or salt form, where R_a, R_b, R_c, R_e and R_h are as shown in the following table

R_a	R_b	R_c	R_e	R_h
H	H	F	OCH_2CH_3	Br
H	H	F	OCH_3	Br
H	Cl	H	OCH_3	Br
H	H	NO_2	OCH_3	Br
H	H	Cl	OCH_3	Br
H	NO_2	Cl	OCH_3	Br
H	F	F	OCH_3	Br
H	CH_3	F	OCH_3	Br
H	H	F	OCH_3	CN
F	H	F	OCH_3	CN
Cl	H	Cl	OCH_3	CN
H	H	Br	OCH_3	CN
H	CH_3	Cl	OCH_3	CN

and R_d, R_f, R_g and R_i are each hydrogen.

6. A compound according to any one of the preceeding claims for use as a pharmaceutical.

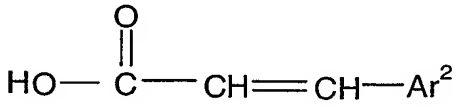
7. A pharmaceutical composition comprising as active ingredient a compound according to any one of claims 1 to 5, optionally together with a pharmaceutically acceptable diluent or carrier therefor.

8. Use of a compound according to any one of claims 1 to 5 for the manufacture of a medicament for the treatment of a condition mediated by CCR-3.

9. Use of a compound according to any one of claims 1 to 5 for the manufacture of a medicament for the treatment of an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease.

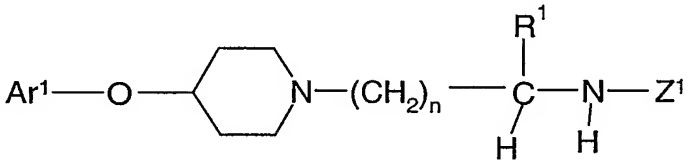
10. A process for the preparation of compounds of formula I which comprises

(i) reacting a compound of formula



II

or an amide-forming derivative thereof, where Ar^2 is as hereinbefore defined, with a compound of formula



III

where Ar^1, R^1 and n are as hereinbefore defined and Z^1 denotes a solid phase substrate chemically linked to the indicated nitrogen atom, and detaching the resulting product from the substrate to replace Z^1 by hydrogen ; and

(ii) recovering the product in free or salt form.

INTERNATIONAL SEARCH REPORT

Intern ! Application No
PCT/ER 01/11628

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/46 A61K31/495 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
5 February 2002	12/02/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Herz, C

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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